The European Multicenter Study on Cyanoacrylate Embolization of Incompetent Great Saphenous Veins

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Disclosures last 12 months

Sapheon: study compensation, stocks
Covidien: study compensation, consultant fees
Cooltouch: research support

Approval Status

CE marked in EU since September 2011,
approved in Canada since January 2014,
not yet in USA – pivotal trial PI Nick Morrison
Objective

Introduction of a novel technique for occlusion of Refluxing GSVs based on Cyanoacrylate Adhesive

Requiring

- no tumescent anesthesia
- no routine postinterventional compression
- Causing no postprocedural paresthesia
Medical devices for different non-venous indications already approved as:

PeriAcryl, GluStitch, Xoin, Gesika, VetGlu, Vetbond, LiquiVet, Indermil, LiquiBand®, Histoacryl, and Truefil®
published Studies on Cyanoacrylate Vein Embolization

Cyanoacrylate Adhesive for the Closure of Truncal Veins: 60-Day Swine Model Results

Jose I. Almeida, MD¹, Robert J. Min, MD², Rod Raabe, MD³, D. J. McLean⁴, and Monte Madsen, RVT⁵

Abstract

Background: The introduction of cyanoacrylate (CA) within a blood vessel triggers polymerization, followed by an inflammatory reaction. Methods: A sheath was positioned 2.0 cm caudal to the junction of the superficial epigastric and abdominus rectus veins in 2 swine, followed by ultrasound-guided injection of 0.16 mL of CA glue. After glue delivery, the catheter was pulled back 3 cm, compression was applied to the treatment site, and the process was repeated for the entire length. At 60 days postimplantation, the veins were harvested surgically and examined histologically. Results: The histologic changes were consistent with a chronic foreign-body-type inflammatory response. Venous closure, segmental wall thickening, and fibrosis were observed. Conclusion: Injection of CA is feasible for closure of superficial veins in animal models. Vein closure is achieved via an inflammatory process which ultimately leads to fibrosis.

Almeida JL, Vasc Endovascular Surg 2011
First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence

Jose I. Almeida, MD, Julian J. Javier, MD, Ed Mackay, MD, Claudia Bautista, MD, and Thomas M. Proebstle, MD, Miami, Naples, and St. Petersburg, FL; La Romana, Dominican Republic; and Mainz, Germany

Objective: The primary objective of this study was to assess the feasibility of an endovenous cyanoacrylate (CA) adhesive implant, delivered with a catheter-based administration system engineered with a nonstick surface, for the treatment of incompetent great saphenous veins (GSVs). The primary safety end point was the rate of serious adverse events related to the procedure. The primary efficacy end point was vein occlusion during follow-up. Secondary end points included the rate of all adverse events and the change in Venous Clinical Severity Scores (VCSSs).

Methods: Thirty-eight incompetent GSVs in 38 symptomatic patients were treated by catheter deployment of CA under follow-up at 1, 3, and 6 months, respectively. Kaplan-Meier analysis yielded an occlusion rate of 92% at 12 months of follow-up. Side effects were generally mild and self-limited, most frequently, phlebitis in six patients (15.8%) requiring nonsteroidal anti-inflammatory drugs for an average of 5.7 days. Eight patients (21.1%) showed thread-like thrombus extensions into the common femoral vein of a mean length of 12.6 mm (range, 3.5−35 mm), which resolved spontaneously without anticoagulation. VCSS improved in all patients from a mean of 6.1 ± 2.7 at baseline to 1.5 ± 1.4 at 12 months (P < .0001). Edema improved in 34 legs (89%) at the 48-hour follow-up. At the 12-month follow-up, and without addi-
Two-year follow-up of first human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence

Jose I Almeida¹, Julian J Javier², Edward G Mackay³, Claudia Bautista⁴, Daniel J Cher⁵ and Thomas M Proebstle⁶

Abstract

Objectives: To evaluate the safety and effectiveness of endovenous cyanoacrylate-based embolization of incompetent great saphenous veins.

Methods: Incompetent great saphenous veins in 38 patients were embolized by cyanoacrylate bolus injections under ultrasound guidance without the use of perivenous tumescent anesthesia or graduated compression stockings. Follow-up was performed over a period of 24 months.

Result: Of 38 enrolled patients, 36 were available at 12 months and 24 were available at 24 months follow-up. Complete occlusion of the treated great saphenous vein was confirmed by duplex ultrasound in all patients except for one complete and two partial recanalizations observed at 1, 3 and 6 months of follow-up, respectively. Kaplan-Meier analysis yielded an occlusion rate of 92.0% (95% CI 0.836–1.0) at 24 months follow-up. Venous Clinical Severity Score improved in all patients from a mean of 6.1 ± 2.7 at baseline to 1.3 ± 1.1, 1.5 ± 1.4 and 2.7 ± 2.5 at 6, 12 and 24 months, respectively (p < .0001). Edema improved in 89% of legs (n = 34) at 48 hours follow-up. At baseline, only 13% were free from pain. At 6, 12 and 24 months, 84%, 78% and 64% were free from leg pain, respectively.

Conclusions: The first human use of endovenous cyanoacrylate for closure of insufficient great saphenous veins proved to be feasible, safe and effective. Clinical efficacy was maintained over a period of 24 months.
The European multicenter cohort study on cyanoacrylate embolization of refluxing great saphenous veins

Objective: Cyanoacrylate (CA) embolization of refluxing great saphenous veins (GSVs) has been previously described. The outcomes from a multicenter study are still lacking.

Methods: A prospective multicenter study was conducted in seven centers in four European countries to abolish GSV reflux by endovenous CA embolization. Neither tumescent anesthesia nor postinterventional compression stockings were used. Varicose tributaries remained untreated until at least 3 months after the index treatment. Clinical examination, quality of life assessment, and duplex ultrasound evaluation were performed at 2 days and after 1, 3, 6, and 12 months.

Results: In 70 patients, of whom 68 (97.1%) were available for 12-month follow-up, 70 GSVs were treated. Two-day follow-up showed one proximal and one distal partial recanalization. Three additional proximal recanalizations were observed at 3-month (n = 2) and 6-month (n = 1) follow-up. Cumulative 12-month survival free from recanalization was 92.9% (95% confidence interval, 87.0%-99.1%). Mean (standard deviation) Venous Clinical Severity Score improved from 4.3 ± 2.3 at baseline to 1.1 ± 1.3 at 12 months. Aberdeen Varicose Vein Questionnaire score showed an improvement from 16.3 at baseline to 6.7 at 12 months (P < .0001). Side effects were generally mild; a phlebitic reaction occurred in eight cases (11.4%) with a median duration of 6.5 days (range, 2-12 days). Pain without a phlebitic reaction was observed in five patients (8.6%) for a median duration of 1 day (range, 0-12 days). No serious adverse event occurred. Paresthesia was not observed.

Conclusions: Endovenous CA embolization of refluxing GSVs is safe and effective without the use of tumescent anesthesia or compression stockings. (J Vasc Surg: Venous and Lym Dis 2014;1:1-6.)
Methods

- 0.09 ml of cyanoacrylate each injection
- first injection 5 cm from SFJ
- second injection 1 cm below first injection
  then every 3 cm
- polymerization time:
  initial injection: 3 minutes
  afterwards 30 s polymerization time
Results
typical clinical picture
1 day after study
treatment of right GSV
Inclusion Criteria

- Age ≥18 years and ≤ 70 years of age.
- Symptomatic primary GSV incompetence diagnosed by clinical symptoms, with or without visible varicosities, and confirmed by duplex ultrasound imaging.
- CEAP classification of C2, C3 or C4
- Ability to walk unassisted.
- Ability to attend follow-up visits.
- Ability to understand the requirements of the study and to provide written informed consent.
- GSV on standing pre-procedure ultrasound ≥3mm and ≤10mm (maximum diameter).
Exclusion Criteria

• Life expectancy < 1 year.
• Regular pain medication.
• Anticoagulation including Heparin or Coumadin.
• Previous DVT.
• Previous superficial thrombophlebitis in GSV.
• Previous venous treatment on target limb.
• Known Hyper-coagulable disorder.
• Conditions which prevent routine vein treatment like: acute disease, immobilization or inability to ambulate, and pregnancy.
Exclusion Criteria

... continued

- Tortuous GSV, which in the opinion of the Investigator will limit catheter placement. (no 2 primary access sites allowed).
- Incompetent ipsilateral small saphenous or anterior accessory great saphenous vein.
- Known sensitivity to the cyanoacrylate (CA) adhesive.
- Current participation in another clinical study involving an investigational agent or treatment, or within the 30 days prior to enrollment.
study characteristics

• Enrollment from Dec 2011 to Jul 2012
• 7 sites involved – total N=70 patients
  - Thomas Proebstle, Germany  n = 20
  - Jens Alm, Germany  n = 15
  - Sameh Dimitri, UK  n = 11
  - Lars Rasmussen, Denmark  n = 10
  - Mark Whiteley, UK  n = 7
  - James Lawson, Netherlands  n = 4
  - Alun Davis, UK  n = 3
patient characteristics

- follow-up: median 6 months [range 3 - 12]
- age: median 48y [range 22 - 72]
- BMI: median 26.0 [range 18.9 – 39.0]

- Max GSV diameter: median 8.0 mm [range 2.5 – 14]
patient characteristics

CEAP baseline

- C2  n = 29
- C3  n = 33
- C4  n = 8
Results

Median GSV length treated
38 cm [range 7-72]

Median CA volume delivered
1.3 ml [range 0.4 - 2.2]

corresponding
to a median number of
injections of
N = 14 [range 4 - 24]
Results

All 70 patients technical successful (100%)

Recanalizations (all partial)

48h $n = 2$ proximal (25 cm) + distal (20 cm)

3 months $n = 2$ 2 proximal (12 + 25 cm)

6 months $n = 1$ proximal (20 cm)

until 12 months follow-up stable, connected to tributaries, no impact on clinical symptoms
12 Months Results
Survival free from recanalization

92.9 %
Results

Improvement of VCSS after study treatment

<table>
<thead>
<tr>
<th>Time after treatment (patients at risk)</th>
<th>VCSS, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (70)</td>
<td>4.3 (2.3)</td>
</tr>
<tr>
<td>Month 1 (70)</td>
<td>1.7 (1.5)</td>
</tr>
<tr>
<td>Month 3 (70)</td>
<td>1.2 (1.3)</td>
</tr>
<tr>
<td>Month 6 (70)</td>
<td>1.0 (1.2)</td>
</tr>
<tr>
<td>Month 12 (68)</td>
<td>1.1 (1.3)</td>
</tr>
</tbody>
</table>
Results
time course of AVVQ score

N = 70 70 70 70 68
Results - Side Effects

• no severe adverse events were observed
• (peri-)phlebitic reaction in n = 8 (11.4%) patients
  median duration 6.5 days (range 2-12)
  only 2 on NSAIDs
• Pain in n= 5 (8.6%) patients
  median duration 1 day (range 0 -12)
  n = 4 patients received NSAIDs
Results - Side Effects

• n = 1 patient (0.7%) with thread-like thrombus extensions across the SFJ at 48h follow-up protrusion length was 0.6 cm

resolved without specific treatment
Gold abstract award for excellence is hereby presented to

Thomas Proebstle, MD, PhD

for his abstract presented at the 2013 UIP World Congress titled
One-Year-Follow-Up of the European Multicenter Study on
Cyanoacrylate Embolization of Incompetent Great Saphenous Veins

SEPTEMBER 8-13, 2013
MEETING DATES

MELVIN ROSENBLATT, MD, FACPh
VeClose Randomized Control Trial

VenaSeal Sapheon Closure System vs Radiofrequency Ablation For Incompetent Great Saphenous Veins

PI: Nick Morrison, Phoenix, AZ, USA

CAUTION: This device has not been approved for sale by the FDA. It is pending a clinical investigation and FDA review.
Study Design

- Pivotal, randomized 1:1 study
- Up to 12 Clinical Sites
- 220 patients (110 per arm) 1:1 randomization
- Up to 244 subjects (including up to 24 roll-in subjects)
- FU period for each patient: total of 36 months
- 9 visits/patient
  - Baseline, Procedure, Day 3, 30 days, 3 month, 6 Month, 12 Month, 24 Month, 36 Month
- Subjects are randomized on the day of the procedure.
- **Adjunctive therapies not allowed until after 3 Month visit**
  - Phlebectomy, foam sclerotherapy
1 Month Data
Closure (as interpreted at investigator sites)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number with Patency (&gt;5 cm)</th>
<th>Complete Recanalization</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFA (n=114)</td>
<td>15</td>
<td>4/15</td>
<td>86.8%</td>
</tr>
<tr>
<td>VenaSeal (n=108)</td>
<td>0</td>
<td>NA</td>
<td>100%</td>
</tr>
</tbody>
</table>

Caveats:
- Study primary endpoint at 3 months will be interpreted by core lab
- Decreased number of patent vessels in RFA group by 3 mo
1 Month Data
Venous Clinical Severity Score (VCSS) – \( \Delta \) from baseline

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>1 Mo</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFA</td>
<td>5.6 (2.6)*</td>
<td>2.6 (2.0)</td>
<td>-2.9 (2.1)</td>
</tr>
<tr>
<td>VenaSeal</td>
<td>5.5 (2.6)</td>
<td>2.3 (1.7)</td>
<td>-3.2 (2.4)</td>
</tr>
</tbody>
</table>

*mean (SD)

CAUTION: This device has not been approved for sale by the FDA. It is pending a clinical investigation and FDA review.
Conclusion

endovenous embolization with cyanoacrylate glue is ready for routine use

the concept of

• no anesthesia
• no compression stockings and
• and no paresthesia

is attractive to many patients